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THE FOOD CONFERENCE AT HOT SPRINGS

Potentially one of the most important international conferences ever held in any country took place at Hot Springs, Virginia, from May 18 to June 3, 1943. Few conferences have aroused so much enthusiasm among the participants; few have had so poor a press, so that the public, at least in this country, is unaware that recommendations were unanimously adopted by the representatives of forty-four governments which may profoundly affect the kind of a world which will emerge when the war is over. Not only were far reaching recommendations adopted, but the Conference urged governments to act immediately upon them.

The first decision of the Conference was to build upon the work in food and nutrition already accomplished by the League of Nations. Reports on the work of the League were presented to the Conference; they exercised a marked influence on its recommendations. For example, in 1935 the League had urged governments to set up national nutrition committees to study problems of food and nutrition, and to recommend to the appropriate agencies suitable nutrition policies and programs. Such committees existed before the war in at least twenty-three countries and twenty-six British dependencies. Representatives of these committees had met twice in Geneva to exchange views and to profit by experience acquired in other countries. Basing its work on the experience of these committees, the Conference urged each government to set up a national nutrition organization, to provide it with adequate funds and facilities, and to give it authority to bring its recommendations to the attention of the public and to the administrative agencies dealing with agriculture and the framing of economic and social policy. Some national nutrition committees had found that such agencies were badly organized and had insufficient authority. The Conference therefore urged governments to reexamine and, if necessary, to reorganize these agencies and to review their relevant laws and regulations so that the food and nutrition policies recommended by national nutrition organizations might be efficiently carried out.

The result of League discussions on food and nutrition and the setting up of national nutrition committees was a great outburst of activity in these fields of work throughout the world. Dietary surveys were carried out; scientific research was stimulated. Governments took measures to improve the nutrition of their most vulnerable groups; the rapid advances in the science of nutrition began to be applied for human benefit on an ever widening scale. In 1935, in a notable report, the League had set out an account of what was then known of food consumption levels and the prevalence of malnutrition in the countries of the world (Mixed Committee of the League of Nations. The Relation of Nutrition to Health, Agriculture and Economic Policy. Final Report. Series of League of Nations Publications, Geneva, 1937). The new knowledge resulting from the League stimulation enabled the Conference to fill in some of the gaps in the picture.

A short summary of the information available on food consumption levels and the prevalence of malnutrition in various countries may be found in the report of Section I of the Conference. This was prepared by Dr. W. R. Aykroyd, Director of the Nutrition Research Laboratories, Coonoor, S. India, with the help of a small committee.

The League's Mixed Committee drew attention to the fact that there was considerable malnutrition among the lower income groups in the United

States of America and Western Europe, available data indicating that the proportion ranged between 20 and 30 per cent. Section I noted that one third of the recruits examined for military service in this country had been rejected, and that the highest ratio of rejection was found in the worst fed regions.

The report of the Mixed Committee showed that the diets of the great mass of the population in the East were grossly deficient by any standard, and that some 75 per cent of the 1150 million inhabitants in Asia consumed diets far below the standard for health. Section I added that a considerable proportion of India's 400 millions do not get enough to eat, in terms of calories, and that deficiency diseases are widespread. Keratomalacia is the commonest cause of blindness in Southern India, beriberi a frequent cause of infant mortality, while osteomalacia leads in numerous cases to an extreme and painful crippling. The situation is much the same in China which has within its borders one fifth of the human race, and the position has become considerably aggravated by the war. Poor diets and malnutrition reduce resistance to disease; in India for example the mortality of children under ten is five times greater than in countries of Western European civilization. A similar high mortality occurs among children of preschool age in Java.

In Africa, malnutrition and deficiency diseases are rife. The typical diet is poor containing little or no milk, and the intake of protein, fats of animal origin, calcium, and vitamins is low. Hospitals are crowded with patients suffering from tropical diseases which are aggravated by malnutrition, and recovery cannot take place until nutritional balance has been restored.

In Egypt the population is heavily infested with parasites and there is a close relation between hookworm, malaria, and malnutrition.

In Mexico, and in Central and South America, there is widespread food deficiency and malnutrition. Infant mortality and tuberculosis death rates are high; specific deficiency diseases are common in some of these countries.

"Taking the world as a whole," stated Section I, "the picture is one of world-wide underconsumption, leading to malnutrition and its attendant evils. It will be one of the tasks of the proposed United Nations food and agricultural organization to complete the picture in dismal detail and to replace it by a brighter one."

It is pertinent here to inquire into the causes of the Food Conference. Why should such a Conference have been held at all? Why should it have been the first international conference on the postwar world held in wartime?

No doubt one of the causes was the great mass of evidence accumulated since 1935 on food consumption deficiencies and the prevalence of malnutrition throughout the world. The increasing weight of that evidence has penetrated beyond technical circles, reaching and influencing writers, sociologists, politicians, and statesmen. Dietary studies have brought home the fact that poverty and malnutrition go hand in hand.

"The incidence of disease in general and the mortality rate among infants, young children, women in the child bearing period, and indeed among all age groups, are invariably higher in ill-fed than in well-fed populations. Recovery from disease is prolonged when the diet is defective. Countries which consume the best diets have the lowest rates of mortality and the highest expectation of life." (United Nations Conference on Food and Agriculture. Hot Springs, Virginia, May 18 to June 3, 1943. Final Act and Section Reports. United States Government Printing Office, Washington: 1943.)

After reviewing the evidence on the relation of poverty to malnutrition, it is no wonder that Section I expressed itself strongly:

"Malnutrition in varying degrees is found in all classes and countries, but more particularly it is the close and constant companion of poverty, both national and individual. Poverty almost invariably means a poor and insufficient diet, and the latter is the main cause of the disadvantage of the poor in respect of health, so clearly shown by statistics of disease and mortality."

But the principal cause leading up to the Conference was undoubtedly the spectacle of starvation, under- and malnutrition in a world whose granaries were bursting with surplus food which could not be sold and whose towns were crowded with people who could not obtain the food they needed for life and health. This paradox has existed ever since the middle of the eighteenth century when machinery and advances in agriculture made possible the large scale production of food. Before that time famine occurred periodically even in the richest countries, but

afterwards there was no longer excuse for hunger in the midst of plenty. After the first World War, farmers were ruined, food dealers and governments bankrupted by accumulations of food which could not find a market, while millions lacked the purchasing power needed to obtain adequate diets. The condition worsened during the depression years; in desperation governments bought up surpluses, denatured or destroyed wheat, burned tons of coffee, dumped food on foreign markets, threw it down sewers, took every course but the obvious one of making it possible for the hungry to consume the food they needed for health and strength, and, perhaps, for the safety of the state. At Hot Springs many sensed a strong undercurrent of feeling that a civilization in which such paradoxes recur could not long endure, and the feeling was at least partly put into words when the Conference declared:

"There has never been enough food for the health of all people. This is justified neither by ignorance nor by the harshness of nature. Production of food must be greatly expanded; we now have knowledge of the means by which this can be done. It requires imagination and firm will on the part of each government and people to make use of that knowledge."

The Conference also affirmed its belief in man's ability to expand food production and to make it possible for men, women, and children everywhere to obtain adequate diets:

"The Conference . . . declares its belief that the goal of freedom from want of food, suitable and adequate for the health and strength of all peoples can be achieved."

But the delegates fully recognized that this goal could not be reached while the fear of war caused the uneconomic use of food and other resources:

". . . We must equally concert our efforts to win and maintain freedom from fear and freedom from want. The one cannot be achieved without the other. . . . The primary responsibility lies with each nation for seeing that its own people have the food needed for life and health; . . . but each nation can fully achieve its goal only if all work together."

It was also plain that efforts to improve the economics of food could not succeed unless they formed part of a concerted program to expand the whole world economy:

"The first cause of hunger and malnutrition is poverty. It is useless to produce more food unless men and nations provide the markets to absorb it. There must be an expansion of the whole world economy to provide the purchasing power sufficient to maintain an adequate diet for all. With full employment in all countries, enlarged industrial production, the absence of exploitation, an increasing flow of trade within and between countries, an orderly management of domestic and international investment and currencies, and sustained internal and international economic equilibrium, the food which is produced can be made available to all people."

Lest it be thought that the delegates believed in the necessity of settling all these difficult issues simultaneously, the Conference declared:

"The first steps toward freedom from want of food must not await the final solution of all other problems. Each advance in one field will strengthen and quicken advance in all others. Work already begun must be continued. Once the war has been won decisive steps can be taken. We must make ready now."

Acting on this belief, the Conference proceeded to set out the program of work. It resolved to set up by July 15, 1943, an Interim Commission consisting of a representative of each of the governments participating at Hot Springs; to draw up plans for a permanent international organization in food and agriculture; and to formulate for the consideration of the governments a formal declaration embodying the obligations which the Conference believed they must assume if food resources were to be increased and diets improved throughout the world.

The outstanding result of this Conference was that it made specific proposals for the national and international machinery needed

to carry out its recommendations. There was no question of adopting a few harmless recommendations and then separating. The delegates appreciated that they were meeting in wartime, that the war would not be won with the collapse of the Axis powers but must be won also in the economic, social, and political fields. Something of the urgency of the war crept into their deliberations; they demanded immediate action and they left nothing to chance. So the Interim Commission is drawing up plans for the permanent food and agricultural organization which will assist governments to work together to raise the levels of nutrition and the standards of living of their people, improve the efficiency of agricultural production and distribution, and submit periodically to the world community reports on the action taken and the progress achieved.

Directives were set out by the Conference to aid the Interim Commission in drawing up plans for the permanent organization:

> That Commission must consider fully the relation of the organization to the other national and international institutions in food, agriculture and related scientific, economic and other fields, which now exist or which may be established; it must also consider methods of associating it with any such institutions.

Such consideration may lead the Commission, and eventually the permanent organization, very far. If associated at once with existing institutions, the organization may profit from the progress these have made and the resources they possess; it may eventually weave all such institutions into a vast international network for technical training, research, exchange of information and experience, and the use of the resources of the whole network in the development of areas which are backward agriculturally and nutritionally.

> The Commission must also give full consideration to provision for bringing into the permanent organization Governments not represented at Hot Springs.

These are, of course, the governments of neutral and enemy countries. Students of international relations will agree that an international organization cannot be fully effective unless it is worldwide in scope.

When the Interim Commission is considering the functions and duties of the permanent organization it must take account of the promotion of scientific, technological, social, and economic research, and of the collection and dissemination of information and provision for the exchange of services.

The permanent organization will be an agency for the collaboration of governments in the fields of food, nutrition, and agriculture; while its own staff may be small, it should be able, like the League, to bring to a particular country in need of assistance the greatest authorities from the different countries. Provision for the exchange of services may also be interpreted to mean that the family of nations may, through the permanent organization, assist backward regions or countries in a much more substantial way:

> "Governments participating in a common undertaking will wish to collaborate so that levels of food consumption may become more equitable not only among the different sections of the population in a given country but among the several nations of the world as well."

When deciding on its duties and functions the Interim Commission must also take into account the fact that the permanent organization may submit to member governments recommendations on:

> Nutrition, standards of consumption of food and other agricultural products; agricultural production, distribution and conservation; statistics and economic studies in food and agriculture including studies on the relation of agriculture to world economy; education and extension work on food and agriculture; agricultural credit; problems of agricultural population and farm labor.

Should the organization be vested with the power of making recommendations to governments on all of these subjects, it would

exert a powerful influence in economic and social affairs throughout the world.

The Interim Commission must also consider the desirability of assigning to the permanent organization functions in the field of development of agricultural resources and orientation of production, agricultural commodity arrangements, agricultural cooperative movements, and land tenure.

To understand the significance of these studies they must be read in conjunction with the recommendations on the same subjects. For example the long term plan for agriculture is aimed at better nutrition and greater efficiency in production, and the Final Act of the Conference explains that in certain parts of Europe this might mean increasing the production of milk products and decreasing the production of g ains. A recommendation for the orientation of a nation's agriculture in that direction would presumably come within the scope of the permanent organization.

The Conference made several recommendations in regard to cooperative movements.

> In order to make it possible for people to help themselves in lowering costs of production, distribution and marketing, all countries were urged to consider the further establishment of producer and consumer cooperative societies; to examine their laws, regulations, and institutions to determine if legal or institutional obstacles to cooperatives existed and to make desirable adjustments. The permanent organization is expected to collect and make available full information concerning the development of cooperatives in different countries.

Finally, the Conference urged the Interim Commission:

> To consider the initiation of preliminary statistical investigations and research into the problems with which the permanent organization would have to deal.

This is one more instance of the mood of the Conference which felt keenly that no time should be lost in beginning the work.

The Conference recommended that governments should:

> immediately undertake to increase their food resources and improve the diets of their people, reporting periodically to one another through the permanent organization on the state of their national nutrition and on the steps being take for its improvement;
>
> take positive measures to improve the diets of its vulnerable groups: pregnant and nursing women, infants, preschool and schoolchildren, adolescents, workers, low income groups, especially those with large families;
>
> study the relationship between malnutrition and impaired bodily health and vigor, and particularly the role of inadequate diets in the causation of and mortality from the diseases which constitute their chief health problems;
>
> investigate the nutritional and related factors which are necessary to secure health and well being;
>
> ascertain the most effective means of disseminating knowledge of correct feeding among all sections of the population;
>
> undertake immediately to ascertain the prevalence of specific deficiency diseases among their peoples, to deal with them by suitable dietary and therapeutic measures, and take proper steps to prevent their recurrence;
>
> adopt dietary standards based on scientific assessment of the amount and quality of food, in terms of nutrients and distinguish clearly between such standards and the more immediate consumption goals.

The report of Section I cites the dietary allowances of the Food and Nutrition Board of the National Research Council as an example of a modern standard which has been widely accepted.

This description of the results of the Conference is sufficiently lengthy without going into the twenty other recommendations which deal with production, distribution, and like subjects. Yet all of these recommendations are important, serving to give a complete picture of what is expected of governments in the field of food and agriculture both before and after the world has recovered from the immediate effects of the war.

How will the recommendations of the

Conference affect this country? One of the first things we must do is to establish a national nutrition organization if it is decided that one does not now exist.

> That organization will have the responsibility of ascertaining food consumption habits and the nutritional status of different sections of the population; it is to be composed of authorities in health, nutrition, economics and agriculture, together with administrators and consumers' representatives. The government is to provide the organization with adequate funds and to give it authority to bring its recommendations to the attention of the public and to the agencies of government which deal with agriculture and social and economic policy.

It is obvious from the wording of the recommendation that the national nutrition organization is not itself to be an administrative agency. It is to guide food and nutrition policy but not to administer it.

Another task our government will be expected to undertake is to:

> "reexamine and if necessary reorganize existing agencies and review legislation on health, agriculture and nutrition so that food and nutrition policies may be efficiently carried out."

Our national nutrition organization will be expected to:

> "exchange information and experience with and provide assistance to other national nutrition organizations, either directly or through the permanent organization. It must send representatives to meet regularly with representatives of other national nutritional organizations under the auspices of the permanent organization."

Our national organization must be prepared to:

> "report to the permanent international organization on the results of its dietary and nutrition studies and on the success attained in raising the national level of food consumption."

It will also be expected to report on the positive measures it adopted to improve the diets of vulnerable groups.

One of our immediate tasks will be to initiate a vigorous campaign against our chief deficiency diseases. Pellagra obviously comes first and here we will be expected to ascertain the prevalence of the disease, to deal with cases by dietary and therapeutic means, and to take steps to prevent its recurrence.

At present we have far too little information on the prevalence of pellagra; a series of measures will be necessary to obtain that information. In the eradication of pellagra we have a task which calls for the closest collaboration between health and nutrition authorities in state and federal agencies as well as between physicians and health authorities.

Responsible statesmen of the United States of America and of Great Britain have indicated their acceptance of the recommendations of the Conference. As the government which convened the Conference, which was responsible for the preparatory work, and which provided the technical secretariat, ours has a special responsibility to set the pace in implementing the recommendations of the Conference. This will be no light task, and the national administration will be well served if it can count on an enlightened public opinion to support the social and economic measures which are necessary in this country to increase our food resources and improve the diets of all of our people.

In contrast to 1918, when international relations were thought of mainly in political terms, the Hot Springs Conference dealt technically with food, nutrition, and agriculture, subjects of vital interest to men and women throughout the world. It was clear that at Hot Springs the common man and woman held the center of the stage. The Conference painted a picture of how common men and women would profit in diet and health in a postwar world in which nations would act together for the welfare of all.

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SPECIFICITY OF THE ARIBOFLAVINOSIS SYNDROME IN MAN

In a previous review (*Nutrition Reviews* **1,** *194* (*1943*)) the work of several investigators was presented, in which it was shown that marginal vascularization of the cornea could be present in human cases under circumstances that excluded riboflavin deficiency. Recent papers have also expressed considerable skepticism as to the specificity of other clinical signs of riboflavin deficiency.

The case against corneal vascularization as a specific diagnostic criterion is strengthened by recent observations in experimental animals which have shown that at least five other deficiency states may lead to lesions of the same type. György, Eckhardt, and Johnson ("The Biological Action of the Vitamins," *Edited by E. A. Evans, Univ. of Chicago Press, pp. 64, 65* (*1942*)) reported observations indicating that some unidentified component of the B-complex could produce such lesions. Bessey and Wolbach observed them in vitamin A deficiency (*J. Exp. Med.* **69,** *1* (*1939*)); Totter and Day (*J. Nutrition* **24,** *159* (*1942*)) reported corneal vascularization in rats with lysine deficiency and with tryptophane deficiency. The observations on tryptophane deficiency were confirmed by Albanese and Buschke (*Science* **95,** *584* (*1942*)) who noted that the lesions in this deficiency developed much more rapidly than in ariboflavinosis; in pregnant animals they developed even earlier (Albanese, Randall, and Holt, *Science* **97,** *312* (*1943*)). Lesions indistinguishable from those produced by ariboflavinosis were observed by Follis, Day, and McCollum in zinc deficiency (*J. Nutrition* **22,** *223* (*1941*)) and sodium deficiency (*Arch. Path.* **33,** *504* (*1942*)). It is interesting in this connection to note that poisons as well as deficiencies may give rise to corneal vascularization. Some years ago Ginsberg and Buschke (*Klin. Monatbl. f. Augenheilk.* **71,** *385* (*1923*)) produced typical marginal vascularization by the administration of thallium.

These observations help to explain the failure of many human cases of corneal vascularization to respond to riboflavin therapy and indicate a need for caution in interpreting this clinical finding.

Other clinical signs of riboflavin deficiency as summarized by Sydenstricker (*Ann. Int. Med.* **14,** *1499* (*1941*)) are: (1) cheilosis; (2) seborrheic dermatitis which often produces a "shark-skin" like appearance of the skin in the nasolabial folds, before the ears, on the forehead, and on the malar eminences; and (3) a glossitis which gives the tongue a magenta color with flattened papillae. There are two main reasons for believing that these lesions are manifestations of riboflavin deficiency. Cheilosis and seborrheic lesions were produced by Sebrell and Butler (*Pub. Health Reports* **53,** *2282* (*1938*)) in human subjects fed a diet deficient in riboflavin and nicotinic acid; these lesions did not respond to the administration of niacin alone but healed when synthetic riboflavin was given. Furthermore there has been abundant clinical evidence that the signs listed above clear when therapeutic doses of riboflavin (5 to 15 mg. per day) are given to individuals with naturally occurring deficiency disease. This "response to therapy" type of evidence is admittedly unsatisfactory, but it provides the best proof available until laboratory methods capable of evaluating the nutritional status with respect to riboflavin are developed.

Doubt as to the specificity of the lesions first was emphasized when Smith and Martin (*Proc. Soc. Exp. Biol. Med.* **43,** *660* (*1940*)) and later Machella (*Am. J. Med. Sci.* **203,** *114* (*1942*)) observed several patients in whom cheilosis healed when pyridoxine alone was administered. Moreover, 8 of Machella's patients with cheilosis failed to show any significant evidence of regression when riboflavin was administered. Of these, 2 responded subsequently to pyridoxine, one to niacin, 2 to brewers' yeast, 2 to vitamin C,

and one remained unhealed. More recently Machella and McDonald (*Am. J. Med. Sci.* **205,** *214 (1943)*) have reported observations on 20 additional individuals who had the clinical signs of riboflavin deficiency but who were not improved by riboflavin. Five of the 20 patients had cheilosis, 9 had eye lesions, and 6 had glossitis. In three instances more than one lesion was present in the same person. A seborrheic dermatitis was not encountered. None of these patients responded to the daily administration of 6 to 12 mg. of riboflavin even though hydrochloric acid was given to the 6 patients who had an achlorhydria. Two of the subjects with cheilosis also failed to improve with pyridoxine, niacin, and ascorbic acid; one failed to heal with pyridoxine; the lesions uniformly cleared when brewers' yeast was given. Of the 9 patients with corneal manifestations, temporary objective improvement occurred with riboflavin but relapses developed even while the vitamin was still being taken. After riboflavin had failed to cure the glossitis, response to brewers' yeast was obtained in 4 patients and to pyridoxine in one. These results justify Machella's doubts as to the specificity of the ariboflavinosis syndrome.

There is also evidence that cheilosis may not always be a manifestation of any vitamin deficiency as such. Ellenberg and Pollack (*J. Am. Med. Assn.* **119,** *790 (1942)*) described 34 patients with glossitis and fissures at the angles of the mouth who did not improve with riboflavin therapy. Thirty-two of these patients were edentulous and were using artificial dentures. Close scrutiny revealed that angle lesions differed from those seen in riboflavin deficiency in that they were deeply fissured and granulomatous. Ellenberg and Pollack believed that the changes they observed were caused either by impurities in dental plates or by improperly fitted dentures which permitted creasing and sagging of the skin at the corners of the mouth. They thought, however, that the resemblance to the cheilosis of ariboflavinosis was close enough to justify use of the term "pseudoariboflavinosis." Dameshek (*J. Am. Med. Assn.* **121,** *249 (1943)*) has recently restated his belief that iron deficiency may cause "perleche" or cheilosis, and Hecht, Rappaport, and Bloch (*J. Am. Med. Assn.* **113,** *2410 (1939)*) described a patient in whom they thought the lesion had been caused by sensitivity to an eosin dye lipstick.

It is evident, therefore, that cheilosis, a vascularizing keratitis, and magenta tongue with flattened papillae may be found in patients who have diseases other than a deficiency of riboflavin. This knowledge, however, should not be permitted to obscure the fact that human subjects who have been eating deficient diets often have these lesions which do respond to riboflavin. The suggestion has been made that perhaps they occur in patients with riboflavin deficiency but are really caused by deficiencies of unidentified members of the B-complex. According to this idea, riboflavin administration would stimulate the appetite so that the unknown factors could be assimilated from the increased food intake. This possibility cannot be denied with certainty although in many of the clinical observations diets have been controlled so that no extra food was allowed. It is fair to conclude that as far as we know at present, even though they may not be specific, cheilosis, a vascularizing keratitis, magenta tongue, and seborrheic dermatitis of the type described constitute a set of clinical signs which can occur separately or in combination in patients with riboflavin deficiency.

VITAMIN CONCENTRATES IN WAR AND POSTWAR DIETS

For many years students of nutrition have debated the advisability of food fortification. As recently as April 1939 the pros and cons of this question were discussed at

a symposium sponsored by the American Institute of Nutrition (*Milbank Memorial Fund Quart.* **17**, *221* (*1939*)). At that time the speakers who participated in the program were far from unanimous with regard to the advisability of encouraging food fortification. One speaker declared that such a policy is fraught with danger and if fortification is to be looked upon with favor, it would be necessary to "proceed with caution." Another authority spoke definitely against the suggestion and stated that he could see no valid reason for a fortification program unless it could be shown that its objective is the "prevention of deficiency diseases." This man spoke from the viewpoint of public health and preventive medicine. A third, speaking from the viewpoint of dietetics and home economics, advocated the judicious use of fortification, "if it could be properly safeguarded." A fourth speaker, talking from the viewpoint of the administration of the Food, Drug and Cosmetic Act, pointed out that, while fortification of specific foods might prove necessary or desirable, the proposal possessed many undesirable, and even dangerous, features. The last speaker, representing the cereal processing industry, advocated that every effort be made to find ways and means of "vitamin retention." He favored "restoration" of vitamins lost in food processing and advocated fortification "when warranted."

Conditions arising from World War II soon brought about the realization that a certain amount of fortification would be desirable, or possibly necessary, to attain adequate intakes of calcium, iron, vitamins A and D, and certain members of the vitamin B-complex. As a result, the Committee on Foods and Nutrition of the National Research Council recommended that the federal government encourage the enrichment of flour and bread (and perhaps corn meal), the fortification of milk with vitamin D, the addition of vitamin A to table fats and of iodine to table salt. Dietary allowances of these and other nutrients as recommended by the Food and Nutrition Board have been summarized in this journal (*Nutrition Reviews* **1**, *164* (*1943*)).

Sydenstricker, whose clinical researches in human nutrition and whose nutrition surveys in Europe, as a member of the Rockefeller Health Commission, have placed him in a position to speak with conviction and authority, raises a number of questions relative to increased use of vitamin concentrates during the present emergency and in postwar relief in Europe (*Nutrition Abstr. and Reviews* **12**, *339* (*1943*)). He points out that, even in peacetime, it is impossible for any nation to ensure an adequate balance between food production and consumption so as to "secure really good nutrition for more than a considerable fraction of its population." He agrees that vitamin concentrates should not be used when natural foods are available in adequate amounts, but emphasizes the fact that we accept as a matter of course the supplementation of infant diets with vitamins.

He states that in time of war it is not sufficient for the average diet to be "just adequate." War workers and members of the armed forces must receive optimal amounts of vitamins; he places children and pregnant women in an equally important classification, owing to the fact that they are more susceptible to temporary deprivation. In support of his belief that the usual service rations do not require supplements of vitamin concentrates, he cites the researches of Keys and Henschel (*J. Nutrition* **23**, *259* (*1942*)) in which it was impossible to show that vitamin supplementation caused good or bad effects on endurance, fatigue, and muscular activity. He doubts the efficacy of high vitamin A intakes for the improvement of night vision of aviators, lookouts, and scouts, and asserts that all evidence indicates that the only individuals who might benefit by such treatment would be those who had been forced to subsist for a considerable time on a diet deficient in vita-

min A or carotene. It is highly unlikely that this could occur in modern armed forces.

In discussing the requirements of industrial workers, Sydenstricker lays considerable emphasis on the importance of adequate (caloric) diets and he favors a high protein intake. Evidence in support of vitamin supplementation, he contends, is far from convincing, and he feels that industrial workers would be better nourished if they received "well balanced snacks" between meals, than to depend on "indiscriminate distribution of vitamin pills."

Sydenstricker believes that the use of vitamin concentrates is indicated for pregnant mothers and for children, particularly in wartime. He points out that such practice is advisable even in peacetime when there are no restrictions on amounts and varieties of foods other than the ability to pay for them. Natural and artificial sources of vitamins A, D, and C are especially important. In addressing his discussion to the British public, he calls attention to the consumption of potatoes and wholemeal bread and expresses the opinion that these foods will probably render vitamin B-complex supplementation unnecessary. British children, he thinks, are better off than any other group of the civilian population, although he states that there may be a need for higher intakes of vitamin C by British children of school age. In view of the shortage of natural sources of vitamin C, he advocates the use of crystalline ascorbic acid, should this become necessary. He deplores the indiscriminate dosing of children with mixed vitamin concentrates, stating that such practice has no clinical or experimental support.

When he considers postwar nutrition problems he adopts a somewhat different view. It is pointed out that different problems will present themselves in various countries because of differences in food habits and in availability of various types of foods. Clinical manifestations during periods of malnutrition will depend on the types of foods available.

Using Spain as an example of what may be expected in other countries, he discusses the types of diets that were available for the civilian population at the start of the Spanish Civil War in 1936. Caloric intakes as low as 600 were observed and 950 calories per day were considered an average figure for people in Madrid. Protein intakes were low, protein was indigestible and of poor biologic value. Diets were poor in minerals and in vitamins A and C. In spite of this, gross deficiency diseases did not occur for more than a year. Scurvy was rare and famine edema did not occur for nearly two years. However, beriberi and pellagra eventually became endemic.

In discussing the food situation in occupied Europe, Sydenstricker states that no definite information is available. All evidence points to the fact that Germany is systematically stripping all occupied countries of good sources of proteins and fats. While there will be insufficient food and inadequate supplies of protein, vitamins A, C, and D, riboflavin, and calcium, he does not expect frank pellagrous and neuritic syndromes to occur on a large scale, except in those areas where they were common before the war.

He agrees that stores of wheat, skim milk powder, dehydrated butter, dried meat and fish (and possibly whale oil and soybean products) should be ready for postwar food relief. The use of vitamin concentrates, under these conditions, is open to question. Consequently, Sydenstricker is inclined to advocate the use of brewers' yeast and crude liver extracts, since they are rich in many members of the B-complex. This does not preclude the use of specific crystalline vitamins or vitamin concentrates when administered by experienced medical personnel.

He terminates his excellent summary of postwar food problems by repeating that there is no substitute for a good diet of natural foods. High extraction wheat flour

is a "must" so far as Europeans are concerned. This flour is used in Great Britain in preference to enriched white flour. Furthermore, he feels that margarines should be fortified with vitamins A and D. The most urgent need will be for protein and calories. Vitamin concentrates must be available because epidemics of vitamin deficiency are bound to occur.

The science of nutrition has made many significant advances since World War I. While postwar food relief problems will be enormous compared with those of 1918, there is every reason to believe that the Allied nations will be in a better position to cope with them, as a result of information gained through researches of the past twenty-five years.

FAT ABSORPTION IN SPRUE AND JEJUNOILEITIS

That the normal postabsorptive increase of fat in the blood following a fat-containing meal fails to occur in active cases of sprue, was shown by Barker and Rhoads (*Am. J. Med. Sci.* **194**, *804* (*1937*)). Such studies, however, have been few in number and, furthermore, have not been carried out to any great extent in other conditions characterized by chronic diarrhea or by extensive inflammation of the small intestine.

An interesting comparison of fat absorption in cases of sprue and of jejunoileitis is reported by Adlersberg and Sobotka (*Gastroenterology* **1**, *357* (*1943*)). They employed a fat tolerance test and a vitamin A tolerance test. For the former the total serum lipids were measured before and four hours after ingestion of 1 g. of butterfat, given as heavy cream, per kilogram of body weight. The vitamin A absorption was measured by determining the vitamin A content of the serum when the subject was fasting and also four hours after the ingestion of a test dose of vitamin A. Usually 3 ml. of percomorph oil was given as the test dose (180,000 I. U. vitamin A). The Carr-Price reaction was used for the measurement of vitamin A.

In 5 active cases of sprue no significant increase in the serum lipids occurred and, in the 2 cases of sprue in which studies are reported, the serum vitamin A was actually lower four hours following the test dose of percomorph oil than before its ingestion. In normal individuals the increase in serum lipids following a test dose ranged from 25 to 129 per cent, averaging 59 per cent. The increase in serum vitamin A in the same individuals ranged from 40 to 336 per cent, except in one instance in which it was only 4 per cent (average, 53 per cent).

In 5 cases of jejunoileitis, on the other hand, both serum lipids and vitamin A increased substantially. The serum lipids increased 20 to 102 per cent, averaging 65 per cent, and the serum vitamin A rose 25 to 274 per cent, averaging 52 per cent. (It is to be noted that some of the variation in the degree of increase in vitamin A was probably due to failure to use a uniform test dose of vitamin A).

That fat absorption should be good in a condition in which there is extensive inflammatory change in the small intestine, as in jejunoileitis, whereas it is poor in sprue, is possibly of great significance in regard to the fundamental nature of sprue. Similar studies should be made in chronic ulcerative colitis, in other forms of chronic diarrhea, and in pernicious anemia. One view concerning the pathogenesis of sprue holds that there is in this condition some functional disturbance in the mucous membrane of the small intestine and that this may be caused by the lack of some essential enzyme or hormone. The improvement in fat absorption which Adlersberg and Sobotka as well as Barker and Rhoads observed following administration of liver extract

favors such a view but, since between them they studied only five cases, their observations are too few to warrant final conclusions. Of further interest in this connection is the rise of blood vitamin A found in patients with sprue when lecithin was fed simultaneously with vitamin A (Adlersberg and Sobotka, *J. Nutrition* **25,** *255* (*1943*)).

The study of fat absorption in cases of intestinal disturbance has been handicapped by the lack of a simple method of study. The vitamin A absorption test is so simple a procedure that it deserves further study and application in the study of problems relating to the function of the gastrointestinal tract.

UREA AS PARTIAL PROTEIN REPLACEMENT FOR RUMINANTS

Vitamins are not the only synthetic materials which may be used as supplements to natural foodstuffs. Recent investigations show that urea can be utilized by ruminants as a supplementary source of nitrogen for the improvement of low protein rations.

Nutritionists have long entertained the idea that nonprotein nitrogen might replace a part of the protein in livestock feeds. Early evidence ruled out this possibility for monogastric animals, but indicated a limited synthesis of nitrogenous compounds by microorganisms normally present in the paunch of ruminants. In the United States interest in this subject first centered around the usefulness of the amide nitrogen of immature hays and grasses. Further interest, especially in Europe, where protein is relatively expensive, centered around the utilization of simple nitrogen compounds such as urea or ammonium bicarbonate. Conflicting results were forthcoming from Europe. These have been reviewed by Krebs (*Biedermanns Zentr. B. Tierernähr.* **9,** *394* (*1937*)) who states that many of these data were inconclusive owing to the fact that the experiments were of short duration or that the levels of protein fed were in themselves sufficiently high to preclude a need for nitrogen from simple supplementary compounds such as glycocoll, urea, or ammonium salts.

Recent experiments conducted in this country with calves, sheep and lambs, dairy cattle, and beef cattle indicate definitely that nitrogen from urea can be used for at least a partial supply of the protein nitrogen. Hart, Bohstedt, Deobald, and Wegner (*J. Dairy Sci.* **22,** *785* (*1939*)) obtained favorable growth with calves when urea nitrogen constituted 43 per cent of the nitrogen of the ration. The nitrogen of ammonium bicarbonate was also found to be well utilized. Analyses of the body tissues at the end of the experiment indicated that the increments in weight were of normal composition.

Harris and Mitchell (*J. Nutrition* **22,** *167* (*1941*)) found that sheep may be maintained in body and nitrogen equilibrium for well over one hundred days on rations containing urea and minimal amounts of protein which provided only one-tenth the amount of nitrogen needed for nitrogen equilibrium. Further experiments on lambs (*J. Nutrition* **22,** *183* (*1941*)) showed that the addition of urea to a low nitrogen ration, that was in itself unable to support appreciable growth, or even to maintain nitrogen equilibrium consistently, converted it into a ration capable of promoting a normal or nearly normal rate of growth.

Work and Henke (*Proc. Am. Soc. Animal Production p. 404* (*1939*)) working in Hawaii where urea has long been used as fertilizer in the cane fields, also found that dairy heifers apparently utilized urea satisfactorily for growth when it was added to a low protein control ration.

More recent experiments by Rupel, Bohstedt, and Hart (*Annual Report of the Direc-*

tor, Agr. Exp. Sta., Univ. of Wis., Bull 453, p. 15 (1941)) and Rupel, Bohstedt, Wegner, and Hart (*Ibid. Bull. 430, p. 20 (1940)*) showed that urea gives about the same results as linseed oil meal for milking cows when it is used as a supplement to a low protein ration made up of timothy hay, corn silage, ground corn, and oats. The results of two years of work by these investigators indicate that urea-fed cows were equal to those which received linseed meal, with respect to milk production, breeding efficiency, and general well-being. Three pounds of urea were used for each 97 pounds of grain, making the total nitrogen content equal to that of a ration containing 18 per cent protein.

The utilization of urea and other simple nitrogen compounds apparently takes place through the growth of bacteria in the rumen. These microorganisms synthesize amino acids and protein from the rumen contents. The bacterial cells then pass from the rumen to the fourth stomach where they are digested and the resulting products of hydrolysis become available to the animal. Obviously such a process can take place only in ruminating animals.

The conversion of urea to protein thus requires a suitable substrate for the development of an active bacterial flora. This includes a fermentable carbohydrate such as starch, to serve as a readily available source of energy for the microorganisms (Mills, Booth, Bohstedt, and Hart, *J. Dairy Sci.* **25,** *925 (1942)*). In addition, a suitable level of protein in the rumen ingesta is required to attain maximum utilization of urea. Wegner, Booth, Bohstedt, and Hart (*J. Dairy Sci.* **24,** *835 (1941)*) have shown that the rate of conversion of urea nitrogen to protein decreases as the protein level of the rumen ingesta becomes greater than 12 per cent, and that the rate and extent of urea conversion decrease as the level of dietary protein is increased to a level higher than 18 per cent. A low protein content in the rumen ingesta is therefore favorable for bacterial protein production from urea.

The level of dietary protein and the amount of urea necessary for maximum utilization of urea are, therefore, important practical considerations. In their experiments with calves which were fed relatively high amounts of urea Hart and co-workers noted some diuresis accompanied by an increase in blood urea. With beef cattle, Work, Hamre, Henke, and Harris (*J. Animal Sci.* **2,** *166 (1943)*) report no evidence of kidney damage at the lower levels of urea feeding, and suggest that for cattle a harmful level of urea intake may be between 2.29 and 2.8 per cent of the dry matter of the ration. On the other hand, Harris and Mitchell report no evidence of kidney damage, other than renal hypertrophy, in lambs fed as much as 3.16 per cent of urea on the dry basis. Apparently there is little danger of obtaining toxic effects, due to urea, if the previously mentioned conservative relationships of urea to dry matter are maintained.

It is possible that the rate of bacterial synthesis may not be of sufficient magnitude, on high urea levels, to satisfy the protein requirements for maximum growth. Conclusive evidence is lacking on this point. However, results presented by Wegner and co-workers (*J. Dairy Sci.* **24,** *51 (1941)*) indicate that bacterial synthesis is relatively rapid since urea, when ingested in amounts of from 1 to 5 per cent of the dry matter of the ration, disappeared from the rumen in from four to six hours after feeding.

It would appear that if the use of urea is to be recommended as a supplement to home grown rations, the amount required would be between 1 and 3 per cent of the dry matter of the ration. The practicability of the use of urea in the feeding of ruminants would depend not only on its availability and price, but also on the availability and price of natural sources of protein.

VITAMIN C DEFICIENCY IN RELATION TO BONE AND MUSCLE INJURY

The relation of both vitamins C and D to normal bone physiology has caused confusion in the literature concerning the relation of the individual factors to the reopening of partially healed fractures. Preliminary results of Kodicek and Murray failed to reveal any tendency for the callus to reopen either in vitamin C or D deficiency. However, in a study covering a longer period of time, these authors (*Nature* **151**, *395 (1943)*) did note other bone and muscle changes following bone fracture which were related to vitamin C deficiency.

The fibulas of 300 g. guinea pigs were fractured. These animals received 1 mg. of ascorbic acid daily, which was sufficient to maintain normal growth. Fourteen days later when the callus had been formed, the animals were divided into four groups. Seven control animals received vitamin A and D concentrate and 10 mg. of ascorbic acid daily; a second group of 12 animals received only a small amount of vitamin D by substitution of carrots for the vitamin A and D concentrate; the third group (4 animals) received 0.5 mg. of ascorbic acid, and later in the experiment 1.0 mg., but adequate vitamin D; and the fourth group (16 animals) were made partially deficient in both vitamins C and D.

On the twelfth day of the experiment an attempt was made to fracture a fibula of each animal with special forceps, but without incision. This was not always successful, but x-ray photographs showed various degrees of damage due to this treatment. There was no evidence of reopening of the callus in any case nor any signs of rickets even in the low vitamin D animals. When the animals were killed seventy-five to ninety days after institution of the diets, certain bone and muscle changes were present in 3 of the 4 animals deficient only in vitamin C, and in a lesser proportion (number not stated) of the larger group deficient in both vitamins C and D. The completely normal appearance of the bone and muscle in the animals deficient only in vitamin D led to the belief that the pathology to be described is related to a chronic vitamin C deficiency.

The bone changes consisted in a marked overgrowth (hyperostosis) of subperiosteal bone of an inferior type. The original bony cylinder displayed a porosis typical of scurvy. Resorption of the old bone and deposition of new periosteal bone apparently occurred simultaneously. The leg muscles showed a swelling with overgrowth of connective tissue. During life the hyperostosis was commonly associated with stiffness in the knee joints and pain upon flexion of the leg. At death the legs were often fixed in flexion.

In one case a hyperostosis was noted in an uninjured leg, and in another the leg immobilization occurred in the uninjured limb. Unfortunately Kodicek and Murray apparently failed to investigate a series of animals on the same diet but without injury. That the pathology described was associated principally with the injury rests on the usually normal character of the uninjured limb. Nevertheless, the earlier findings of Mouriquand that chronic vitamin C deficient guinea pigs show periosteal thickening and ankylotic changes suggest that the above pathology may also be present to some extent in uninjured animals.

From the clinical standpoint, the authors cite the observations of Ellis in which periosteal thickening of both ulnas occurred in an infant considered deficient in vitamin C. It is also pointed out that the animals which developed the changes could be considered only to have a mild vitamin C deficiency, hence special attention might be usefully directed toward an adequate vitamin C intake after bone and muscle injury in man.

PITUITARY CYSTS IN VITAMIN A DEFICIENT CATTLE

Madsen, Hall, and Converse (*J. Nutrition* **24,** *15* (*1942*)) have emphasized that cysts of the pituitary gland occur as a frequent, highly interesting, and important manifestation of vitamin A deficiency in young cattle. Description of these cysts has also been made by L. A. Moore (*Ibid.* **17,** *443* (*1939*)) and by Sutton, Krauss, and Hansard (*J. Dairy Sci.* **23,** *574* (*1940*)), but apparently they have not been observed in any other animals. They occur either in the residual lumen between the anterior and posterior lobes of the pituitary or within the body of the posterior lobe itself. They occasionally are sufficiently large to cause compression of the gland and injury to the glandular parenchyma. Madsen and associates found cysts in 13 of 15 young beef and dairy cattle who were either suffering from vitamin A deficiency or who were known to have had a severe vitamin A depletion early in life. That this incidence is highly significant is suggested by the fact that only four or five cystic pituitary glands were found in 10,000 pituitaries collected from apparently normal cattle. The deficient animals showed varying degrees of blindness and occasionally convulsions or papilledema.

The history of one of the animals suggests that the cyst was large enough to impair pituitary function permanently. This cow was depleted of vitamin A for one hundred and twenty-five days beginning on the twenty-third day of life and developed papilledema, low blood carotene, low blood vitamin A, convulsions, diarrhea, night blindness, and slow growth. When the carotene content of the ration was increased, the deficiency manifestations disappeared and the animal became apparently healthy except that growth was abnormal. It conceived at 18 months of age and aborted during the eighth month of pregnancy. At autopsy four days later a cystic pituitary gland was found which had replaced a considerable portion of the anterior lobe; a large part of the remaining glandular parenchyma was taken up by fibrous tissue. Many of the glandular cells had pyknotic nuclei and appeared nonfunctional.

The mechanism by which the cysts are produced is not clear, but they apparently should be considered a part of the pathology of vitamin A deficiency in cattle. If pituitary cysts prove to be characteristic of vitamin A depletion in cattle alone, they will be interesting enough. The possibility does exist, however, that other animals may be found to show the same abnormality.

HUMAN REQUIREMENT OF RIBOFLAVIN

There has been little exact information about the daily requirement of riboflavin for man. Sebrell and Butler were able to induce ariboflavinosis in human subjects with diets that provided about 0.5 mg. of riboflavin per day (*Pub. Health Rep.* **54,** *2121* (*1939*)). That amount, therefore, appears to be inadequate. It is also fairly well established that the daily allowance of 1.8 to 3.3 mg. recommended by the Food and Nutrition Board of the National Research Council is sufficient for the healthy adult. No satisfactory data have existed to help fill the gap between these two figures, however, until the recent studies by Williams, Mason, Cusick, and Wilder were published (*J. Nutrition* **25,** *361* (*1943*)). These workers observed chemical evidences of progressive depletion of tissue stores of riboflavin when subjects were allowed only 0.35 mg. of the vitamin per 1000 calories; by the same criteria, 0.8 mg. per 1000 calo-

ries maintained tissue stores while 0.5 mg. per 1000 calories permitted depletion to a slight degree.

The subjects selected by Williams and associates were female inmates of the Rochester State Hospital who engaged regularly in activities such as housekeeping, laundering, and sewing. They had received daily supplements of 2.0 mg. of thiamine, 2.0 mg. of riboflavin, 2.0 mg. of pyridoxine, 5.0 mg. of calcium pantothenate, and 40 mg. of niacinamide for several weeks or months prior to the period of restriction. The restricted diet contained no milk, cheese, eggs, organ meats, legumes, or green leafy vegetables. Approximately 58 per cent of the calories were derived from carbohydrate, 12 per cent from protein, and 30 per cent from fat. The subjects were divided as follows: Group I—4 women in whom riboflavin was restricted to 0.35 mg. per 1000 calories; their diets were supplemented with fortified halibut liver oil, ascorbic acid, thiamine, pyridoxine, calcium pantothenate, niacinamide, inositol, choline chloride, ferrous sulfate, and tricalcium phosphate; Group II—2 subjects who received the same diet but in whom the supplements of thiamine, niacin, pyridoxine, and pantothenic acid were omitted; Group III—2 subjects who were given the basal diet and 1.0 to 3.0 mg. of riboflavin daily in addition to the supplements given to Group I; this diet was adequate in every respect, so far as could be judged; and Group IV—5 subjects who were maintained on a diet which contained 0.5 mg. of riboflavin and 0.45 mg. of thiamine per 1000 calories; it was supplemented with fortified halibut liver oil, ascorbic acid, ferrous sulfate, and tricalcium phosphate. The experimental periods lasted from two hundred forty-six to two hundred eighty-eight days.

Tests of tissue stores of riboflavin were made at monthly intervals by measuring the urinary excretion of riboflavin which occurred during a four hour period after the subcutaneous injection of 2.0 mg. of riboflavin. These determinations indicated that there was progressive depletion of the stores in those subjects who received 0.35 mg. of riboflavin per 1000 calories. The rate of the depletion was not accelerated in Group II, the subjects of which were also deficient in thiamine and perhaps in other vitamins of the B-complex. When the intake was 0.5 mg. per 1000 calories (Group IV), the stores were depleted only to a slight degree, while those subjects who received 0.8 mg. or more of riboflavin per 1000 calories showed no evidence of depletion. Williams and associates, therefore, feel that 0.5 mg. of riboflavin per 1000 calories provides an allowance that is close to the daily requirement of the vitamin.

It is extremely interesting that none of the subjects developed any of the clinical evidences of riboflavin deficiency during the period of study. Furthermore, except in those women in whom a thiamine deficiency was also induced, there were no neurologic disturbances, anemias, alterations of the basal metabolic rate, changes in the electrocardiogram or in gastrointestinal motility, nor any abnormal elevations of blood pyruvic acid, lactic acid, or glucose after administration of dextrose orally or intravenously. The values for calcium, phosphorus, protein, and lipids in the blood remained normal.

The fact that no clinical evidences of ariboflavinosis appeared in the more severely deprived subjects is disturbing, especially since the specificity of the various objective manifestations of riboflavin deficiency has been so effectively challenged (*Nutrition Reviews* **1**, *194* (*1943*)). Cognizance should also be taken of the report by Boehrer, Stanford, and Ryan (*Am. J. Med. Sci.* **205**, *544* (*1943*) that college students who were being treated with a 1000 calorie diet for obesity failed to develop any signs of ariboflavinosis during a period of five weeks when each student was given only 0.47 mg. of riboflavin per day. There are, however, certain significant differences between the subjects studied in these two

investigations and those used by Sebrell and Butler when they induced signs of ariboflavinosis. Sebrell and Butler's subjects were allowed 0.5 mg. of riboflavin per day but had a caloric intake of approximately 2500 calories per day. It is highly probable that the requirement is at least roughly proportional to the caloric value of the diet. Furthermore, as Williams points out, the most severely restricted subjects in his study received 0.7 mg. per day (0.35 mg. per 1000 calories) and had good tissue stores at the start of the period of restriction. Sebrell's subjects probably had a low intake of riboflavin before they were studied. The failure of Williams and associates and of Boehrer *et al.* to induce clinical evidences of riboflavin deficiency should not be interpreted as denying the observations made by Sebrell and Butler. There is a real need, however, for additional studies like those of Williams' not only to increase our knowledge of the daily human requirement of riboflavin but also to restrict riboflavin more severely so that the existence of a clinical syndrome characteristic of ariboflavinosis can be confirmed or clarified.

MASSIVE DOSES OF VITAMIN D IN THE PREVENTION OF RICKETS

A recent report by Wolfe (*J. Pediatrics* **22**, *396* (*1943*)) raises again the question of the value of isolated, large doses of vitamin D in the prevention of rickets in children. A number of years ago it was shown that the intramuscular injection or the oral administration of large amounts of fat soluble D—from 100,000 to 600,000 U.S.P. units of vitamin D—in a single dose would protect an infant from rickets for several months. Some difficulties were encountered in developing preparations that were suitable for injection. But the amounts of crystalline vitamin D required to provide the necessary dosage are small, 1 mg. of crystalline material being equivalent to about 40,000 U.S.P. units of vitamin D, and these difficulties have been more or less overcome. Most of the investigations on this subject have been made by pediatricians in Germany; some work has been done in the United States, but the method of treatment has not gained widespread acceptance by practitioners. An examination of the facts, as exemplified by the report of Wolfe, will reveal that the prophylaxis of rickets with single (or a few) massive doses of vitamin D, though effective and harmless in competent hands, is neither necessary nor desirable except perhaps under unusual conditions.

In harmony with the observations of others, Wolfe has shown the method to be effective in the prevention of roentgenologic signs of rickets in infants. Seventy-five healthy infants were treated and records were obtained on 62 of these patients, most of whom were brought to a dispensary by their mothers for the usual medical check-up, but a few of whom were patients in a pediatric clinic or in private practice. The infants were selected on the basis of having received little or no vitamin D during early infancy. At about the third month of life, roentgenograms were taken and the mothers were given 12 capsules, each containing 50,000 U.S.P. units of vitamin D in the form of activated ergosterol, and instructed to administer the contents of 6 capsules with a small amount of cereal and to repeat the dose on the following day. If the material were regurgitated, this fact was to be reported and more capsules would be supplied. Of the 62 patients under observation, 44 healthy infants showed no roentgenologic or other signs of rickets in a period of from two to seven months. The remaining 18 infants had initial mild rickets as revealed by roentgenograms, and they showed evi-

dence of healing of their rickets during the period of observation. It would thus appear that vitamin D, when administered orally in appreciable amounts, can be stored in the tissues where it serves as a source that can be drawn upon over an extended period of time. From other reports in the literature to which reference is made by Wolfe, it would appear that the vitamin is stored in the skin and subcutaneous fat, in the fat of the kidneys and lungs, and in the nervous system.

Wolfe has suggested two plans of prophylaxis. Recognizing the possibility of harm from large doses of vitamin D to very small infants, it is suggested that the young infant be protected up to the second or third month of life by daily prophylactic doses of 1000 units of vitamin D. At this time the infant can be given a large dose of 600,000 units, which is repeated four or five months later "depending on the clinical findings, the time of the year and the age of the infant. In the summer an older infant may be allowed to go 6 months before repeating the massive dose."

The other suggested procedure is to administer a dose of 50,000 U.S.P. units of vitamin D in milk at the end of the first and second months of life. Subsequent treatment would be the same as in the alternative plan.

While Wolfe and others have called attention to many supposed advantages of the prophylactic treatment of rickets by massive doses of vitamin D, and while they have pointed out the disadvantages of the usual method of giving smaller amounts more in keeping with the nutritional needs of the infant from day to day, the arguments are not convincing. A vast educational campaign for the administration of vitamin D, at least in the winter months, has been conducted in the United States for many years. This educational program has been effective and today there are few mothers, even among the poorest people, who are not acquainted with the values of sunlight, of cod liver oil which contains the "sunshine vitamin," of vitamin D milk both fluid and evaporated, and of various pharmaceutical forms of vitamin D. Wolfe makes the following illuminating statement: "Inasmuch as it had become the established practice to give young infants some antirachitic agent soon after birth, it was not possible at the beginning of this study to enroll infants who had received no antirachitic agent in the form of irradiated evaporated milk or some fish oil." It is true that most infants today receive sufficient amounts of vitamin D to prevent severe rickets; and in order to make his investigation, Wolfe found it necessary to issue detailed instructions to the mothers that vitamin D preparations be withheld from the infants selected for study. Except for the occasional child whose vitamin D requirement is unusually high, it is not uncommon for teaching hospitals to experience difficulty in finding a case of severe rickets for demonstration to medical students. Many cases of rickets do occur, of course, but it is doubtful if the incidence of this metabolic disorder would be decreased by the introduction of an entirely new mode of therapy. The remedy would seem to be the continuation of educational efforts along the lines that have proved eminently successful to date.

There are many questions about the vitamin D requirement of the normal infant which still demand solution. Among these problems is that of ascertaining the optimal amount of vitamin D needed, not only for protection against rickets, but for best growth and development. There is much evidence also to show that vitamin D is an important factor in the formation and protection of the teeth. The advocates of the administration of vitamin D in isolated doses of large magnitude apparently have overlooked the growth and tooth aspects of the vitamin D problem. Until these problems have been studied in detail there is not sufficient evidence to justify an assertion that

the massive dose method of preventing rickets is capable of producing results equal to those that may be obtained with the customary procedure of administration.

FEEDING QUICKLY MOVING TROOPS

When one reads of rapid troop movements, one rarely thinks of the nutritional problems which arise. The so-called U. S. Field Ration A, which is consumed by our troops within the continental limits of this country, requires for 1000 combat troops for five days, 34,200 pounds of food, 10,000 pounds of kitchen equipment, mess kits weighing 1000 pounds, and fuel weighing 1200 pounds, not to speak of 8000 pounds of personnel for the handling of the food, almost 2200 pounds of subsistence for these people, and 322 cubic feet of refrigeration space.

It is obvious that this Field Ration, which is similar to the Garrison Ration of peacetime, is not suitable for rapid movement. Field Ration B, which is the type used for expeditionary forces, differs from Ration A only in that all perishable foods are replaced by nonperishable processed or canned foods. This, however, reduces the total mass of food and equipment only by about 20 per cent.

Field Ration C, which is a sort of emergency ration, eliminates the need for kitchen equipment, mess kits, subsistence personnel, etc., but it is bulky, nevertheless. It consists of six cans per man per day. The cans include meat and vegetable stew, hash or beans, biscuits, soluble coffee, sugar, and hard candy.

Against this background of bulk and weight and in the case of the emergency ration, unattractiveness, the new Field Ration K which is described by Berryman and Chambers (*Gastroenterology* **1**, *335 (1943)*) is impressive. This consists of 3 units, one for each meal, packaged in boxes 6 inches long, 4 inches wide, and 2 inches deep. The boxes are impervious to water, chemical warfare agents, and vermin. The 3 units for the day supply canned ham and egg, canned meat or fish preparations, two types of biscuit, a fruit bar, a chocolate bar (which melts only at a temperature of 120°F. rather than at 95°F. as ordinary chocolate does), a beverage (soluble coffee), bouillon powder, lemon powder, malted milk-dextrose tablets, sugar, chewing gum, and cigarettes. This ration is not fixed, and may be changed from time to time as experience indicates.

This attractive combination of foods weighs only 2.67 pounds per man instead of 5.48 pounds for Ration C and 11.32 pounds for Ration A, and requires no equipment whatever, although hot water may be desirable for the beverage and the bouillon. It supplies 3000 to 3400 calories, 115 g. of protein, 22 mg. of iron, 1000 mg. of calcium, 2000 mg. of phosphorus, 3 mg. of thiamine, 2.5 mg. of riboflavin, 25 mg. of nicotinic acid, and 55 mg. of ascorbic acid. It is stated that this ration is acceptable to the soldier for a longer period of time than any of the other rations yet devised for a similar purpose.

VITAMIN AND MINERAL RETENTION IN COOKING VEGETABLES

Students of home economics and nutrition have long emphasized the desirability of conserving nutrients by cooking vegetables in as little water as possible. Past researches have supported the contention that valuable water soluble nutrients are sure to be lost in appreciable amounts in the drainage water. Most of the vitamin studies in support of this viewpoint have been concerned with vitamin C, since chemical methods were first developed for the estimation of this water soluble food factor.

Oser, Melnick, and Oser (*Food Research* **8**, *115 (1943)*) have recently studied the

effect of "old" and "new" methods of cooking on the retention of five vitamins and three inorganic nutrients in vegetables. Vegetables used in the study were peas, potatoes, carrots, and broccoli since they represented legumes, tubers, roots, and leafy (leaves, stems, and flowers) vegetables, respectively. The vegetables were analyzed before and after cooking and the estimations included carotene, thiamine, ascorbic acid, riboflavin, nicotinic acid, iron, calcium, and phosphorus.

The "old-fashioned" method of cooking involved the use of large proportions of water. Weighed amounts of vegetables were added to cold distilled water and the mixtures were brought to a boil and permitted to simmer until "sufficiently cooked." Steam was permitted to escape freely by adjusting the lid of the cooking pan. Aluminum ware was used in all experiments. The "new method" of cooking involved the use of minimal amounts of water, and cooking was conducted with a minimal loss of steam by keeping the lid of the cooking pan tightly closed. Here again steaming was continued until the vegetables were cooked "sufficiently to serve." No stirring was permitted in any of the cooking experiments.

One pound of vegetable was used in each experiment but the amount of water added depended on the type of vegetable to be cooked. All vegetables (fresh or cooked) were homogenized in a Waring blendor in an atmosphere of carbon dioxide. Measured amounts of water were added prior to homogenization except in the case of the vitamin C analyses, when metaphosphoric acid was added instead of water, to prevent destruction of ascorbic acid by oxidative enzymes.

Carotene was determined colorimetrically, thiamine was assayed by the thiochrome method, vitamin C by the dye titration method, riboflavin by a microbiologic method, and nicotinic acid by a colorimetric method. Iron, calcium, and phosphorus were determined by the official methods of the Association of Official Agricultural Chemists.

The authors point out that, in a few instances, discrepancies occurred, indicating a greater amount of nutrient present in the cooked product than was found in the fresh raw vegetable. Limitations in the precision of analytical methods, difficulty of complete extraction of vitamins from raw vegetables, and possible destructive enzyme action in raw vegetables during homogenization, may be some of the factors causing these discrepancies. In these instances the authors arbitrarily assumed that the nutrient involved was completely retained.

As might be expected, the "new method" of cooking caused greater retention of nutrients than the "old method." In the case of peas 85 to 96 per cent of the vitamins were retained by the new method of cooking. While losses of different vitamins varied, the losses due to the old method of cooking were much greater. For example, thiamine and nicotinic acid losses were from eight to ten times greater when peas were cooked in a large volume of water and drained. Mineral retention was high in peas which were cooked by either method. About the same conclusions can be drawn regarding vitamin retention in potatoes and carrots cooked by new and old methods. However, mineral losses were somewhat greater by the old method.

When broccoli was cooked by either method, significant water soluble vitamin losses occurred, although retention was in favor of the new cooking method. No carotene losses could be noted in either culinary treatment, while thiamine losses amounted to 33 and 53 per cent, respectively, when new and old methods were compared. As much as 64 per cent of the nicotinic acid was lost from broccoli when it was cooked by the old method. Mineral losses in broccoli were appreciable (14 to 19 per cent) by the new method but these were increased to about 28 per cent when more cooking water was used.

These studies furnish additional evidence to support the accepted view that vegetables should be cooked in as little water as possible in order to conserve the maximum amounts of vitamins and minerals, without sacrifice of palatability.

SULFAGUANIDINE, SUCCINYLSULFATHIAZOLE, AND DEFICIENCY DISEASE

Investigations which emphasize the importance of intestinal bacteria in the nutrition of vertebrate animals have been reviewed several times in this journal (*Nutrition Reviews* **1**, *4*, *35*, *175*, *199*, *220* (*1943*)). These reviews described experiments which have shown that intestinal bacteria can synthesize vitamin K and many of the B-vitamins both *in vitro* and *in vivo*. They reviewed evidence which indicates that these synthesized vitamins apparently may furnish a substantial amount of some of the vitamin requirements both of ruminants and of those animals which have large cecums. The rumen and the cecum in these species seem to serve as "fermentation vats." In man, intestinal synthesis may supply all the biotin and vitamin K required. Furthermore, when one of the sulfonamide drugs, particularly one that is poorly absorbed like sulfaguanidine or succinylsulfathiazole, is given orally to certain experimental animals reduction in growth rate or other manifestations of deficiency disease may be produced. It seems probable that the effect of the sulfonamide drugs is to alter the intestinal flora and to interfere, consequently, with the synthesis of vitamins within the intestinal tract. Two of the questions which arise about these relationships are: (1) What type of deficiency is produced when sulfaguanidine or succinylsulfathiazole is given? and (2) What is the specific effect of the poorly absorbed sulfonamide preparation on intestinal bacteria? At least partial answers to both these questions are now available.

Most of the investigators who have studied the deficiencies produced by oral administration of sulfonamides have used white rats fed a synthetic diet. Black, Overman, Elvehjem, and Link (*J. Biol. Chem.* **145,** *137* (*1942*)) demonstrated that inadequacies of vitamin K and of para-aminobenzoic acid were produced. If the synthetic diets containing sulfaguanidine or succinylsulfathiazole were supplemented with thiamine, riboflavin, pyridoxine, niacin, calcium pantothenate, choline, inositol, para-aminobenzoic acid, ascorbic acid, and the fat soluble vitamins, the rats still showed retarded growth. This was corrected by the addition of biotin (Daft, Ashburn, and Sebrell, *Science* **96,** *321* (*1942*); Nielson and Elvehjem, *J. Biol. Chem.* **145,** *713* (1942)). Martin (*Proc. Soc. Exp. Biol. Med.* **51,** *353* (*1942*)) observed that rats fed as outlined above developed silvery-gray coats. This change was reversed by folic acid concentrates. Nielson and Elvehjem found that folic acid also had a powerful growth stimulating action on animals fed in this manner. It is apparent, therefore, that the inclusion of poorly absorbed sulfonamide drugs in synthetic diets of rats has produced deficiencies of vitamin K, para-aminobenzoic acid, biotin, and folic acid.

Welch and Wright (*J. Nutrition* **25,** *555* (*1943*)) in studies which are complimentary, observed that succinylsulfathiazole, when incorporated to the extent of 5 or 10 per cent in a complete diet of natural materials (Wayne or Purina brand), caused no demonstrable effect on the growth rate of rats. However, only 1 or 2 per cent of the same drug was effective in producing marked inhibition of growth when added to purified rations which were supplemented with a vitamin A, D, and E concentrate and with the same crystalline B-vitamins used by Black and associates. Moreover, the animals frequently, but irregularly, developed alopecia, spectacled eyes, panophthalmitis,

porphyrin-caked whiskers, and achromotrichia. A yeast concentrate and a liver extract, both fed at a level of 1 per cent, partially antagonized the effect of the sulfonamide, while an extract of rice polishings was possibly more effective. Dried grass also seemed to supply the missing factors. Addition of 20 micrograms of biotin per 100 g. of the sulfonamide ration had a slight stimulating effect on growth. In other experiments, 2 micrograms of biotin and 10 mg. of "folic acid concentrate" (200,000 Snell-Peterson units per gram) were administered daily to rats by stomach tube. Each of these substances, when given singly in the amounts indicated, had some activity in overcoming the growth depression caused by succinylsulfathiazole; but when they were administered together a striking stimulation of growth resulted. The authors state that a favorable effect on the clinical signs of the deficiency state "was exerted by a combination of the folic acid concentrate and biotin, and occasionally by one or the other factor alone." One gathers from this that the response to each factor, therefore, was apparently not consistent; even so, it is regrettable that a more complete description of the therapy-induced changes was not made. One of the most interesting observations made by Welch and Wright is related to the bleeding manifestations which occurred in some of their animals fed the purified diet containing succinylsulfathiazole. As was to be expected, the prothrombin values of the rats who bled were low. However, the prothrombin returned to normal and the hemorrhages stopped after biotin and the folic acid concentrate were fed. Vitamin K administration was not necessary to bring about this result. It is suggested that the biotin and folic acid stimulated the synthesis of vitamin K by intestinal bacteria. These findings indicate that these two vitamin substances, in addition to being probable essential components of metabolic systems in the rat, function also in promoting a certain type of bacterial synthetic activity.

Spicer, Daft, Sebrell, and Ashburn (*Pub. Health Rep.* **57,** *1559 (1942)*) also observed that the use of sulfaguanidine or succinylsulfathiazole in purified diets fed to rats led to the development of granulocytopenia and anemia which could be cured with whole dried liver or certain liver fractions. Their studies have recently been extended to include the use of three of the more soluble sulfonamides: sulfathiazole, sulfadiazine, and sulfanilamide (Kornberg, Daft, Sebrell, *Science* **98,** *20 (1943)*). The basic ration allowed was composed of glucose (Cerelose), purified casein, cottonseed (Wesson) oil, a salt mixture, and 1 per cent sulfathiazole, sulfadiazine, or sulfanilamide. Supplements of thiamine, riboflavin, pyridoxine, calcium pantothenate, niacin, and choline chloride were fed daily. Fifty-two of 105 rats developed either a severe granulocytopenia (polymorphonuclear granulocyte count of less than 150 cells per cmm.), an anemia (less than 7.5 g. hemoglobin per 100 ml. blood and a hematocrit value under 25 per cent), or both. The changes in peripheral blood were found as early as the tenth experimental day and as late as the eighty-sixth. Animals which remained free of these hematologic abnormalities were observed as long as one hundred and sixty-nine days. The blood dyscrasias appeared in 28 out of 34 animals given sulfathiazole, 22 out of 36 given sulfadiazine, and in only 2 out of 35 given sulfanilamide. Granulocytopenia was twice as common as severe anemia in animals fed sulfathiazole. These frequencies were reversed for sulfadiazine. Therapy with liver extract or whole dried brewers' yeast brought about prompt improvement in the peripheral blood. Unfortunately, the bone marrow changes which accompanied the blood dyscrasias were not described. It would also be of interest to know whether biotin or folic acid concentrate possess therapeutic value for the granulocytopenia and anemia. The mechanism by which these soluble sulfonamide compounds bring about the abnormalities described is not clear. They may, possibly, alter the

synthesis of essential factors by intestinal bacteria as seems to be the case with sulfaguanidine and succinylsulfathiazole. However, as the authors point out, the possibility that the drugs may produce these effects by toxic action, either direct or indirect, is not eliminated. They may interfere with tissue enzyme systems, the integrity of which is restored by some unidentified factors in liver and yeast.

The most consistent change produced in the intestinal flora of animals and men fed sulfaguanidine or succinylsulfathiazole is a reduction in the number of coliform organisms (Corwin, *Bull. Johns Hopkins Hosp.* **69,** *39 (1941);* Poth, *et al. Arch. Surg.* **44,** *187 (1942);* Kirby and Rantz, *J. Am. Med. Assn.* **119,** *615 (1942);* and Gant, Ransone, McCoy, and Elvehjem, *Proc. Soc. Exp. Biol. Med.* **52,** *276 (1943)*). Enterococci are often increased in number so that the total bacterial count per unit of fecal material may not be significantly altered. Gant and coworkers made the interesting observation that the decrease in number of colon bacilli in rats (Sprague-Dawley colony, chosen because of freedom from protozoan and metazoan parasites) began as early as the third or fourth day after feeding with the sulfonamide-containing diet was begun. However, after eleven to twenty-five days the colon bacilli gradually increased and ultimately became as numerous as they had originally been. In spite of this fact, the animals showed no growth. The colon bacilli, therefore, had apparently lost their ability to synthesize the growth promoting factors, presumably biotin and folic acid. Animals fed a succinylsulfathiazole-containing diet supplemented with liver extract or crude folic acid maintained their normal growth in spite of a marked reduction in *E. coli.* These results indicate that normally the colon bacillus is mainly responsible for the synthesis of biotin and folic acid or related growth promoting factors. When sulfonamide drugs, poorly absorbed from the intestinal tract, cause deficiencies of biotin and folic acid to develop, they do so by decreasing the number of *E. coli* in the intestinal tract. The observation by Gant and colleagues that *E. coli* may reappear in great numbers while the sulfonamide is still being administered but then are not able to synthesize biotin and folic acid is important. It needs, however, to be verified.

SUPPLEMENTARY FOOD AND THE NUTRITION OF SCHOOLCHILDREN

The incorporation of all the essential vitamins and minerals in a single or minimum number of food articles is a useful goal if directed toward mass feeding, and particularly if considerable transportation difficulties must be faced. The object of nutrition education in this country, however, has been to advocate a diversified palatable diet so as to include all the essential nutrients. There has, of course, been emphasis on certain foods for special purposes, such as the consumption of citrus fruits for their vitamin C content, dark green leafy vegetables for provitamin A, milk for calcium, riboflavin, protein, etc. There are indeed justifiable instances of food supplementation such as the use of fish liver oils and enriched flour; but indiscriminate supplementation is definitely opposed by the majority of nutritionists.

Nevertheless there are many reports to indicate that a rather large proportion of our people are malnourished and that the most direct solution to the problem is by means of food supplementation. Harris, Weeks, and Kinde (*J. Am. Dietet. Assn.* **19,** *182 (1943)*) are of the belief that a high proportion of schoolchildren that they examined showed evidence of malnutrition and that the situation was improved by feeding a special soup designed to meet, in itself, the daily requirement of vitamins and minerals.

The dehydrated soup mixture developed by Harris *et al.* contains in every 100 g., 10

g. of skim milk powder, 30 g. of low-fat peanut flour, 30 g. of low-fat soya flour, 15 g. of precooked dry peas, and 15 g. of flavors, condiments, etc. The components of the soup are rich in protein and members of the vitamin B-complex, and when supplemented with vitamins and minerals, 1 ounce of the powdered soup contains the average daily allowances of calcium, iron, vitamins A and D, thiamine, riboflavin, niacin, and ascorbic acid. The same portion contains in addition 12.6 g. of protein, 1.6 g. of fat, and 8.5 g. of carbohydrate. The calcium was added as dicalcium phosphate and the carbonate, but no details were given as to which and how much of the other factors were added to meet the desired levels.

One ounce of the dehydrated soup in a cup of hot water results in a product which is mildly flavored, palatable, and well tolerated. The usefulness of this soup as a supplementary food was tested on 760 Michigan schoolchildren approximately 10 years of age. The physical status of the children was checked at the beginning and end of the experiment by physicians especially trained under Drs. Jolliffe and Kruse to detect nutritional deficiency lesions. The children were divided into a "soup" group and control group in the accepted experimental manner. All received the regular school lunch during the three month period of study, February to May. Those in the soup group received a daily portion of the soup equivalent to 1 ounce of the dehydrated product.

A remarkably high percentage of respiratory infections was noted at the first examination; 22 per cent had tonsillitis, 20 per cent rhinitis, 8 per cent pharyngitis, and 4 per cent sinusitis. It was stated that the soup group showed a greater improvement in these conditions during the three month period of study but that the difference could not be established as significant. Certain improvements in skin conditions in both groups were noted and attributed possibly to the change from the winter to the spring season. Although not mentioned by the authors, it would seem that this factor would also be the predominant one in the consideration of respiratory diseases.

The hemoglobin values were increased in those children receiving the supplementation. At the end of the study, 45 per cent of those in the control group had values below 14 g. per cent while 37 per cent of the soup group were below this level. This difference was considered significant.

At the beginning of the study, 50 per cent of the children showed a plasma ascorbic acid level below 0.5 mg. per cent. At the end of the study 43 per cent of the control subjects were still below this figure but only 18 per cent of the soup group remained below this level.

Biomicroscopic examinations of the eye were made for detection of vitamin A and riboflavin deficiencies and for any changes resulting from the supplementation. Relative opacities of the eye were judged as an indication of vitamin A status and the number of capillary "arcades" in the cornea as an index of riboflavin deficiency. The authors were aware of the present uncertainty concerning the significance and specificity of biomicroscopic findings for these purposes. It was nevertheless concluded that 50 to 55 per cent of the children showed evidence of vitamin A and riboflavin deficiency. Although there were individual instances of improvement in the riboflavin status among the group receiving the soup supplement, no really significant differences between the groups could be determined. One must agree with the authors that it is unfortunate that the experiment could not have been continued for a longer period, both for the sake of the experiment itself and for the larger problem of the relation of these much discussed pathologic lesions to vitamin deficiency.

Harris and co-workers conclude that these children, in spite of a regular school lunch, had a low nutritional status. This conclusion depends largely on the plasma

ascorbic acid, hemoglobin, and biomicroscopic findings. In order to evaluate this conclusion, the criteria used must be examined. Biomicroscopic findings and the nature of the pathology considered characteristic of ariboflavinosis are under too much justified comment to draw a conservative opinion as to the prevalence of true riboflavin deficiency. As for the plasma ascorbic acid criterion, there does not exist a unified opinion as to what level to accept as normal or adequate. For example, no direct evidence can be provided to show that individuals with levels of 0.3 to 0.6 mg. per cent ascorbic acid show any signs of deficiency of this nutrient or are in worse health than those who are more nearly saturated with this vitamin. Even "normal" hemoglobin values, particularly in children, are subject to periodic revision.

The evidence is therefore certainly not overwhelming that these children had such a low nutritional status. This is supported by the fact that the soup supplementation, providing the daily allowances of the various factors, did not produce any startling results. The only readily apparent effects, those on the hemoglobin and vitamin C status, could undoubtedly have been duplicated by simple iron and vitamin C therapy. No other "significant" effects, including height and weight changes, were even claimed. The value of this compact nutritive food for use in starving countries and bread-line feeding is probably considerable, but a useful role in American dietetics is less obvious.

AMINO ACIDS AND PLASMA PROTEINS

The unique medical problems which develop during wars have often stimulated scientists to perfect surgical technics, to study more intensively the etiology and control of specific infectious diseases, and to investigate the fundamental physiologic disturbances in special conditions like shock. It is rather interesting, therefore, to observe that the current need for a plasma substitute and the great interest in shock has apparently accelerated investigations of amino acid metabolism and of the nutritional significance of plasma proteins. In many cases these subjects were, of course, being studied before the war began. In 1934, Holman, Mahoney, and Whipple demonstrated that homologous plasma protein given by vein apparently supplied all body needs for protein (*J. Exp. Med.* **59,** *269* (*1934*)). It was further shown that plasma protein is in dynamic equilibrium with tissue proteins and can either make them or be formed from them (*Physiol. Rev.* **20,** *194* (*1940*)). Then clinicians became interested in the possibility of maintaining nitrogen balance and of stimulating the formation of plasma proteins by administering mixtures of amino acids as the principal or sole source of nitrogen. Because pure amino acids were difficult to obtain, hydrolysates of casein were used instead. It was established that nitrogen balance could be maintained with casein hydrolysates even when the material was given intravenously (*J. Am. Med. Assn.* **112,** *796* (*1939*); *J. Pediatrics* **15,** *469* (*1939*); *J. Pediatrics* **16,** *679* (*1940*); *Am. J. Med. Sci.* **200,** *239* (*1940*); *J. Clin. Invest.* **22,** *257* (*1943*)). Elman demonstrated that parenteral administration of the hydrolysates led to regeneration of plasma proteins (*Ann. Surg.* **112,** *594* (*1940*); *Arch Surg.* **44,** *1064* (*1942*)). These accomplishments represent significant progress. But many workers interested in the problems have dropped other research projects in order to speed up their search for a satisfactory plasma substitute. It is the nutritional observations which have resulted, sometimes as "by-products," which concern us here.

Madden and associates, for instance, have

shown that mixtures of the ten amino acids known to be adequate for growth in rats can produce new plasma proteins in abundance (*J. Exp. Med.* **77**, *277* (*1943*)). The dogs used in these experiments were depleted of plasma proteins by plasma withdrawal (red blood cells were replaced). The ten amino acids which made up the mixture were threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, methionine, histidine, and arginine. They were as effective when given by vein as by mouth and as the sole source of protein derivatives were able to maintain health and nitrogen equilibrium for periods as long as six weeks. Caloric, salt, and vitamin requirements of the animals were met by basal diets which provided various combinations of sucrose, corn starch, corn oil, Crisco, bone ash, a salt mixture, the fat soluble vitamins, and yeast or the available crystalline vitamins of the B-complex. The aggregation of these ten amino acids when given orally (roughly 16 to 18 g. per day) produced about 15 g. of plasma protein per week, and hence compared favorably with standard food proteins fed by mouth (4 g. of liver and 8 g. of thymus produce approximately 1 g. of plasma protein). More globulin than albumin was produced, but this was also true when proteins were fed.

The withdrawal of one or more amino acids from this mixture of ten led to less favorable responses. Either the production of plasma protein decreased, or the nitrogen balance became negative and the clinical state of the animals deteriorated. Not all possible combinations of withdrawal were tried, but the statement holds for those experiments that were done. Omission of glycine led to a slight loss of body weight even though good plasma protein production continued and the nitrogen balance remained positive. Omission of arginine caused least disturbance of any of the combinations tested; there resulted a slow fall in plasma protein production but no weight loss occurred and the nitrogen balance was normal. When threonine or valine was withdrawn, there followed a loss of appetite, negative nitrogen balance, and a rapid fall in plasma protein formation. When the mixture was fed without the trio of histidine, lysine, and arginine, nitrogen balance was maintained for as long as one week but plasma protein production fell toward zero. For short periods of time, cystine could be substituted for methionine without causing any change in plasma protein production, but weight loss occurred and the clinical condition of the dog declined. Choline would not prevent this effect. The behavior of cystine in some experiments was difficult to understand. At times it apparently acted as a stimulant in the reaction leading to plasma protein production.

Madden points out that while a mixture of these ten amino acids is effective, it is possible that the inclusion of other amino acids, proline for instance, might increase the nutritional value of the mixture. It is interesting that intravenous injection of these combinations of amino acids caused no reactions, and in that respect they are probably superior to many of the casein hydrolysates which have been used.

Direct evidence for the incorporation of amino acids into newly synthesized plasma protein has been obtained by Seligman, Fine, and associates (*J. Clin. Invest.* **22**, *265*, *275* (*1943*)). These workers, in their study of traumatic shock, wanted to follow the movement of plasma into and out of the circulation. They accordingly synthesized cystine, homocystine, and methionine which contained radioactive sulfur. When these amino acids were fed to hypoproteinemic dogs, plasma protein was produced which contained the radioactive amino acids and was, therefore, tagged. The results have nutritional significance because cystine was utilized more completely than were methionine and homocystine and appeared in higher concentrations in plasma protein. The rapidity of synthesis is indicated by the fact that maximum concentrations of the

radioactive amino acids occurred in plasma protein within twenty-four hours.

Schoenheimer, Ratner, Rittenberg, and Heidelberger (*J. Biol. Chem.* **144,** *541* (*1942*)) have tagged leucine, glycine, and tyrosine with heavy nitrogen. They demonstrated the incorporation of these "labeled" amino acids into plasma protein of normal rats and determined that the rate of synthesis was comparable to the rate of synthesis of proteins in the liver, kidney, and intestinal tract. All fractions of plasma protein contained about the same amounts of the isotopic amino acids. Schoenheimer interprets his results as confirming the idea expressed above that plasma protein is in dynamic equilibrium with the proteins of other tissues.

Robscheit-Robbins, Miller, and Whipple (*J. Exp. Med.* **77,** *375* (*1943*)) studied the simultaneous production of hemoglobin and plasma protein in dogs (1) which were fed abundant iron and protein-free or low protein diets and (2) in which a sustained anemia had been produced by systematic bleeding. These animals efficiently used serum digests, hemoglobin digests, and casein digests when given both orally and intravenously to make hemoglobin and plasma protein. These materials maintained a positive nitrogen balance. Dog plasma and the same amino acid growth mixture used by Madden were employed. All substances listed led to the production of more hemoglobin than plasma protein, and the amino acid mixture favored hemoglobin production more than did any of the digests. In all experiments 1.5 to 4.0 g. of hemoglobin were produced for every gram of plasma protein formed. It is interesting that this ratio held also for plasma and for serum digests. Plasma was, however, a more efficient producer of both hemoglobin and plasma protein than were serum digests. Casein digests formed as much new plasma protein as did the other material tested (plasma excepted). Hemoglobin digests were effective producers of plasma protein. These results show clearly that plasma proteins can contribute to the building of hemoglobin and indicate that, when the need exists, hemoglobin can contribute to the formation of plasma proteins. The authors speculate that hemoglobin production is possibly favored because normally there is three times as much hemoglobin as plasma protein in the dog's circulation.

A somewhat disturbing observation about the nutritive value of injected plasma has been made by Elman and Davey (*J. Exp. Med.* **77,** *1* (*1943*)). These authors injected intravenously 3 g. of protein as plasma per kilo per day for one week into dogs who had been made hypoalbuminemic by a non-protein diet. This required the daily injection of about 50 ml. of plasma per kilo, an amount in excess of the actual circulating plasma. The injection was well tolerated and produced both a rise of plasma albumin to levels above normal and an increase in plasma volume. In spite of the fact that a diuresis occurred, the urinary nitrogen was not influenced. There was, therefore, complete retention of the protein and a remarkable positive nitrogen balance. From 9 to 13.5 per cent of the administered plasma remained in the circulation; the rest apparently was taken up by the tissues. However, during the two weeks following the plasma infusions, there was a marked increase in the excretion of urinary nitrogen. In one experiment, this was great enough to wipe out all of the nitrogen retained during the week of plasma injections. Elman believes these results indicate that the body does not permanently utilize plasma proteins as nitrogenous nourishment when they are injected in such large amounts. He points out that administration of a similar amount of nitrogen given as hydrolyzed casein was not followed by an increased excretion of urinary nitrogen. While these results are at variance with the observations of Holman, Mahoney, and Whipple, the work is not strictly comparable to other reported experiments because of the large quantities of plasma used by Elman and Davey. This

work, however, introduces the need for further clarification of the nutritional utilization of plasma proteins under varied conditions of administration.

EFFECTS OF VITAMIN A DEPLETION IN MAN

The need for careful studies on the nutritional requirements of man is well recognized. In some instances experimentally induced vitamin deficiencies have provided valuable information as to the symptomatology and the correlation of laboratory studies and clinical findings. The need for the latter is especially great.

The effect of vitamin A deficiency in man has been studied by several different groups of investigators (*Nutrition Reviews* **1**, *66, 78, 176 (1943)*), who in most instances attempted to correlate the clinical findings with dark adaptation or blood vitamin A levels. As is well known, it has not been possible from these studies to establish a conclusive relationship between either dark adaptation or blood vitamin A levels and the nutritional status of the subjects. Recently, Brenner and Roberts (*Arch. Int. Med.* **71**, *474 (1943)*) have investigated the effect of vitamin A depletion in four women and two men, 20 to 24 years of age, for a period of 31 and 20 weeks respectively. The diet was adequate except for vitamin A which was present in the amount of 67 to 100 U.S.P. units per day. The following studies were carried out in an attempt to detect the effects of vitamin A deficiency: (1) measurement of dark adaptation twice weekly with the biophotometer, the Hecht adaptometer, and the regenometer (the latter was used only during the last few weeks of study); (2) weekly (occasionally biweekly) blood vitamin A and carotene determinations; (3) total white cell and differential counts; (4) microscopic examination of skin taken from the lateral external portion of the thigh by biopsy after four and seven months of depletion; (5) slit lamp examination during the last week of the experiment; (6) blood vitamin A levels after ethyl alcohol ingestion during the last week of the experiment; (7) visual field determination by perimetry. Most of the studies were initiated a few weeks before the subjects were placed on the deficient diet.

The results of all the different measurements revealed no significant changes from those found prior to the deficiency. Unfortunately, the failure to examine the eyes of the subjects with the slit lamp before the vitamin A deficient diet was instituted makes it difficult to assess the significance of the minor eye changes observed in some of the subjects during the last week on the diet. The general health of the subjects was as usual and there were no complaints of night blindness.

The blood carotene level dropped sharply after the first few weeks on the diet and then continued to drop more slowly to a very low level. In contrast, the blood vitamin A levels remained practically unchanged. Wald, Brouha, and Johnson (*Am. J. Physiol.* **137**, *551 (1942)*) previously noted that subjects saturated with vitamin A did not develop signs of vitamin A deficiency after a period of about six months on a diet with vitamin A content of 100 I.U. or less daily. On their diet, the vitamin A content of the plasma remained high throughout the experimental period, although the plasma carotenoids quickly dropped from normal levels to as low as 0.5 micrograms per ml. Brenner and Roberts therefore confirm the belief that the carotene content of the blood varies directly with the dietary intake, while the vitamin A level, with the exception of small fluctuations, may remain constant for long periods of depletion. It would appear that the body is able to draw extensively upon its stores of vitamin A and that deficiency does not develop until these stores are sufficiently depleted to cause a drop in the blood vitamin A level, and therefore a decrease in the amount of the vitamin available for tissue utilization.

The importance of the body stores in relation to the rate of development of vitamin A deficiency is indicated by the fact that the majority of deficiency cases occur in infants. In children, the amount of vitamin A storage is less than in adults. It has been estimated that the vitamin A depletion period in very young infants is three to four months and in children more than 1 year of age it is twice this long. Clausen (*Med. Clin. N. A.* **27,** *349* (*1943*)) reports that in Denmark during the last great war when so many of the dairy products and fresh green vegetables were being exported, an epidemic of xerophthalmia developed in children.

While Brenner and Roberts noted no increased incidence of colds, it was observed that the blood vitamin A levels dropped to about one-half the initial value when all the subjects caught colds. With the subsidence of fever, the blood levels returned to normal. The well recognized decrease of blood vitamin A levels in the presence of infection (or fever) raises the question as to whether the presence of infection (or fever) causes a great utilization of vitamin A, or whether the mechanism for mobilization from the liver is impaired. In view of the fact that the blood vitamin A levels returned to their original levels on subsidence of fever, it would appear that the latter explanation is more likely.

As a measure of the reserve of vitamin A in the liver, the subjects ingested 75 to 100 ml. of ethyl alcohol just before termination of the experiment. Clausen and associates (*Science* **93,** *21* (*1941*)) previously found that vitamin A present in the liver could be mobilized by oral administration of alcohol. Brenner and Roberts were able to confirm this finding with their subjects. They found that the alcohol administration resulted in a noticeable rise, four hours after consumption, in the vitamin A level of the blood. It is doubtful whether this phenomenon can be of much practical use in the diagnosis of vitamin A deficiency, in view of the evidence that deficiency does not develop as long as the liver stores are sufficient to maintain the blood vitamin A at normal levels. Where it is suspected that depression of the blood vitamin A level may be due to infection or some other circumstance not associated with depletion of the liver stores, a test, based upon the ability of ethyl alcohol to mobilize the vitamin A in the liver, might however be of value in making a differential diagnosis.

Some of the subjects showed marked lymphocytosis several times during the experimental period, but no subject demonstrated the blood picture described by Abbott, Ahmann, and Overstreet (*Am. J. Physiol.* **126,** *254* (*1939*)) in vitamin A deficiency. This consisted of a decreased total white blood cell count with a lymphocytosis characterized by predominance of the large over the small lymphocytes and with many juvenile and stab forms and degenerate cells. Rather marked variations in the blood lymphocyte content, as detected by counts performed at intervals during a several months' period, is not an unusual finding in normal persons even in the absence of demonstrable infection or deficiency disease.

The interpretation of all the findings by the authors suggests that either the subjects had sufficient stores to withstand the effects of depletion, or that the usually associated signs of vitamin A deficiency are not merely the results of an uncomplicated vitamin A deficiency. With regard to the former point, the authors have calculated that on the basis of reported vitamin A values in human liver and the assumption of a rate of utilization of 2000 U.S.P. units daily, it would take from one to two years to completely deplete the liver of its vitamin A stores. As regards the latter point, there is evidence that poor dark adaptation and phyrnoderma (toad skin) may occur in deficiency states other than vitamin A. (Stewart, *Edinburgh M. J.* **48,** *217* (*1941*); Moore, *J. Trop. Med. & Hyg.* **44,** *47* (*1941*)).

It is apparent from this study that the human adult may have a considerable re-

serve of vitamin A and that low blood vitamin A levels, poor dark adaptation, and phrynoderma cannot be relied upon as early signs of vitamin A deficiency.

VITAMIN REQUIREMENTS OF ANIMAL STRAINS

Apparently, vitamin requirements for strains of animals within a species may vary. This complicating factor has been observed in both chicks and white rats. Lamoreux and Hutt (*J. Agr. Research* **58,** *307 (1939)*) found that white Leghorn chicks survived longer on a diet deficient in thiamine than did Rhode Island Reds. More recently the same authors (*Genetics* **28,** *79 (1943)*) studied two strains of white Leghorn chicks which differed in their relative resistance to a deficiency of riboflavin. The chicks were fed a diet deficient in riboflavin but adequate with respect to all other nutritive requirements. Resistance to the deficiency was measured by the ability to survive and gain weight during the first few weeks after hatching. One hundred ninety-one chicks of the fifth generation in the resistant strain made an average gain in weight that was 36 per cent greater than that shown by 50 chicks of the susceptible strain. Furthermore, during the same period, 29 per cent of the chicks in the susceptible group and only 6 per cent of those in the resistant strain died. Females were consistently more resistant than males.

Light and Cracas (*Science* **87,** *90 (1938)*) noted that three different strains of white rats in their laboratory differed in growth response to the inclusion of graded amounts of thiamine in experimental diets (2, 4, and 8 micrograms daily). That these strain differences were inherent was indicated by the fact that the young of the animals all responded to thiamine administration in a manner characteristic of each parent strain.

Engel (*Proc. Soc. Exp. Biol. Med.* **50,** *193 (1942)*) observed that different litters of weanling white rats varied in their requirement for choline. The experimental diet was composed of 30 per cent peanut meal, 6 per cent alcohol extracted casein, 54 per cent sucrose, 4 per cent of a salt mixture, and 6 per cent lard; supplements of thiamine, riboflavin, pyridoxine, calcium pantothenate, carotene, and calciferol were added. The experimental ration was given at 23 days and hemorrhagic kidney disease, shown by Griffith and Wade to be characteristic of choline deficiency in rats (*Proc. Soc. Exp. Biol. Med.* **41,** *188 (1939)*), developed within two weeks. The addition of 4 mg. choline per day protected the rats of some litters but was inadequate for others. Male rats were more susceptible to the kidney lesion than were females. In a continuation of these studies, Engel (*Proc. Soc. Exp. Biol. Med.* **52,** *281 (1943)*) mated male and female rats having a high requirement and animals having a low requirement for choline. The choline needs of the progeny of these two strains were then studied. With a daily intake of 4 mg. of choline chloride, 100 per cent of the males of the "high choline requirement" (HCR) strain developed kidney hemorrhage and 58 per cent of them died. With the same dietary level of choline, the incidence of hemorrhage among males of the "low choline requirement" (LCR) strain was only 48 per cent while the mortality was 10 per cent. Females again required less than males. Preliminary studies indicated that the daily requirement for choline in the HCR strain was about twice as great as in strain LCR.

These results indicate that in different strains of chicks and rats the daily requirement for at least three vitamins may vary. The variations in requirement, moreover, are inherited. Males seem to need greater amounts than females. Observations of this kind indicate the importance of recording the strain of animals in nutrition investigation and they call attention to the care which must be exercised when results with one strain of animals are compared with those of another strain. Species differences in response to specific nutritional deficiencies are confusing enough. If animal strain differences should prove to be common, the task of the animal investigator will be greatly complicated.

NOTES

Ascorbic Acid in Home Canned Tomato Juice

Since home canning of tomato juice will become even more popular this year, data as to type of container and method of extraction so as to best retain the ascorbic acid content are of value. Hauck (*J. Home Econ.* **35**, *295* (*1943*)) reports the effect of such variations. Tin canned juice retains a higher vitamin content than does the juice held in glass. The difference was marked in samples stored for from two and one half to eight and one half months. In unlined tin the value fell from 19.7 mg. per cent to 16.1, in glass from 19.0 to 5.7, and in enamel-lined tin cans from 17.7 to 14.0 at the eight and one half months period. Neither the amount of headspace in glass and tin containers nor protection from light by the tin appeared to account for the difference.

Cold expression of the juice from the tomatoes, with or without previous heating of the pulp, resulted in no better preservation of ascorbic acid in the home canned juice than did the expression of the juice from the hot pulp.

The Diet of Ancient Egypt

The diet of ancient Egypt is of special interest because numerous skeletal remains of its population are available, and from a study of these skeletons we know that most of the diseases which beset us today were known at that time. Tubercular bones, Pott's disease, periostitis, osteomyelitis, numerous fractures and dislocations, especially skull injuries, achondroplasia, and many congenital deformities were common. The incidence of dental caries in early Egypt was 10 per cent which comes close to the best record for dental health, which is shown by the Eskimos, among whom caries occur in only 6 per cent of the population, the lowest in any human group.

The longevity record for Egyptians could not have been too bad, since the figures indicate that in Roman Egypt 73.7 per cent of the population was dead by 40 years of age, while in Austria in the nineteenth century the equivalent figure was 66.2 per cent. Curiously enough, scurvy and rickets were very uncommon.

This is of special interest if we consider the diet of those people. According to Sir Armand Ruffer, bread and vegetable oil were the staples of the bulk of the population. Egypt was known as the bread-eating nation. Barley and wheat flour were used. Baking was a large industry, but home baking was also common. Confectionery and bread of fine flour were available as was also a bread from ricinus, a common remedy against diarrhea. The army ration was 4 pounds of bread a day. Some meat was also consumed, but because the cow and bull were sacred they were killed only for sacrifice. Sheep and pigs were also sacred and not eaten. Hyenas, on the other hand, were fattened for the table. Little milk was consumed and it was used mainly as a sacrifice and occasionally as sacred medicine. The most common meat was that of geese and a few other fowls, but even that was eaten only on rare occasions. Fish was consumed by the common people but not by the priests, and was regarded as polluting food. The eel was worshipped, which fact is referred to in a poem cited in Athenaeus.

"I never could myself your comrade be
For neither our manner nor our laws
Agree with yours, but they are wholly different.
You do adore an ox. I sacrifice him
To the great gods in Heaven. You do think
An eel the mightiest of divinities
But we do eat him as the best of fish."

Some fruit, such as figs, dates, and melons were occasionally eaten, but very few vegetables, among which can be cited the roots of the lotus and papyrus, beans, lentils, onions, and garlic. Asparagus and artichokes were considered rare delicacies for the rich.

Oil was extracted from a number of vegetables and was regarded like cotton in the

South or sugar in Cuba. The Ptolemies made a government monopoly of the oil trade and prohibited foreign importation of it. Oil was made of linseed, pumpkins, castor beans, and olives and was used for cooking, lighting, as food, embalming, and for cosmetics.

The lack of green and yellow vegetables in the diet may account for the frequency of eye diseases in Egypt. Herodotus and others were impressed by the number of eye doctors there. Where their vitamin C came from is not clear.

Vitamin A Units

As an expression of vitamin A potency, the International Unit and that of the U. S. Pharmacopeia Commission have been accepted as interchangeable. This, however, does not appear to be true, as indicated by a series of exhaustive tests reported by Hume, Secretary of the "Vitamin A Sub-Committee of Accessory Food Factors Committee of the Lister Institute and Medical Research Council" (*Nature* **151,** *535 (1943)*). The U.S.P. reference oil has always officially borne the value of 3000 I.U. per gram, which was the value found by test against the 1931 mixed carotene standard. A more recent cooperative retest carried out by the Vitamin A Sub-Committee revealed a value of 2619 instead of 3000 I.U. per gram for this oil. The U.S.P. and I.U. units are therefore not exactly equal, the former being only 2619 to 3000 or seven eights of the latter. This may result in some confusion; but since the difference does exist, its existence is better recognized.

Palatability of Natural Foods

An arrangement of foods in preferential order is described by Dove (*J. Nutrition* **25,** *447 (1943)*). The object of this study was to determine preference values since in the last analysis this is an important and frequently neglected factor in considering nutritive value. Preference value may be used for subsequent correlations with other nutrient values of the same varieties or species of food; further correlation with survival, production rate, efficiency, or other physiologic characteristics of the organism; and an analysis of the nature of the palatability difference. Dove contends that from the orderly arrangement of palatability differences other important positive and negative characteristics of foods may be detected.

In this preliminary report the rabbit served as the subject. Six varieties of clover, four varieties of alfalfas, four varieties of sweet clover, fifteen varieties of cabbages, and three varieties of kale were tested for their acceptance value in terms of fresh, green weight. Enlargement of this study obviously is necessary in order to make such data of practical value.

Peeled Wheat

Sealock and Livermore (*J. Nutrition* **25,** *265 (1943)*) have investigated the merits of a new type of whole wheat bread. The wheat from which this bread was made was produced by the new "flotation process of Earle" and is known as "peeled wheat." It contains 98 per cent of the original weight of the wheat kernel since only the thin epidermis or "beewing" is removed. The peeled wheat bread furnishes thiamine, riboflavin, and nicotinic acid in amounts equal to the upper level recommended by the Food and Nutrition Board of the National Research Council. Vitamin values for the peeled wheat bread, expressed as milligrams per 100 g. are: thiamine 0.3, riboflavin 0.25, nicotinic acid 3.5, pantothenic acid 0.52, pyridoxine 0.31, and inositol 64.4. Rat feeding experiments indicated this bread to be slightly superior to whole wheat or white bread for growth.